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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/776,252	02/02/2001	Andrew Ellington	D 6 2 9 6	9740

7590 03/29/2002

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EXAMINER	
ZITOMER, STEPHANIE W	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 03/29/2002 6

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/776,252	ELLINGTON, ANDREW	
	Examiner	Art Unit	
	Stephanie Zitomer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 February 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Sequence Communication* .

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SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
09/776,252	2-2-2001	ELLINGTON	D6296

EXAMINER	
S. ZITOMER	
ART UNIT	PAPER NUMBER
1634 ~~1655~~	6

DATE MAILED:

Please find below a communication from the EXAMINER in charge of this application.

Commissioner of Patents

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Applicant is given ONE MONTH, or THIRTY DAYS, whichever is longer, from the mailing date of this letter within which to comply with the sequence rules, 37 CFR 1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). In no case may an applicant extend the period for reply beyond the SIX MONTH statutory period. Direct the reply to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the reply.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephanie Zitomer whose telephone number is (703) 308-3985. The examiner can normally be reached on Monday through Friday from 9:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152. The official fax phone number for this Group is (703) 308-4242. The unofficial fax number is (703) 308-8724. The examiner's Rightfax number is 703-746-3148.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196. For questions and requests relating to formal matters contact Patent Analyst Tiffany Tabb at 703-605-1238.

S Zitomer

Stephanie Zitomer, Ph.D.

PRIMARY EXAMINER
ART UNIT 1634

DETAILED ACTION

Informalities

1. The disclosure is objected to because of the following informalities:

(a) In the figure descriptions (pages 9-11) each descriptive paragraph must initially identify all parts of the collective figure, that is, begin, e.g., "Figure 1A and 1B..." and the paragraph must further identify and describe, e.g., Figure 1A and Figure 1B. The latter requirement appears to have been done for all figures except Figure 1.

(b) Citations at page 5, lines 6 and 8, are incomplete.

(c) The sequences shown in Figures 2A and 2B do not have SEQ ID NOS: as required by 37 CFR 1.821-1.825. The SEQ ID NO: of each sequence may be in the figure or in the figure description.

(d) The application is not in compliance with 37 CFR 1.821-1.825 regarding applications containing nucleotide sequences. See the accompanying Notice to Comply.

Appropriate correction is required.

Objection the specification: Lack of antecedent basis

2. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: The negative limitation in claim 10 "wherein the aptamer is not a...biopolymer" is not found in the specification. Antecedent basis must be provided by amending the specification, for example, in the definition of " aptamer: at page 14 or at the bottom of page 4 where "biopolymer receptors" are mentioned.

Rejections under 35 U.S.C. 112, second paragraph: Indefiniteness

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) The claims are confusing overall because it is unclear whether the method is for detecting the presence of a ligand by detecting a change in signal from a reporter-

bearing signaling aptamer resulting from binding of the aptamer to the ligand or for transducing a change in the signal from a signaling aptamer comprising a reporter molecule by producing a change in conformation of the signaling aptamer comprising the reporter molecule. It is suggested to clarify the claimed method.

(b) In the preamble and method steps "reporter molecule" ("fluorescent dye") lacks antecedent basis in that it has no recited relationship to "signaling aptamer". It is suggested to recite that the reporter molecule is attached to, part of or comprised by the signaling aptamer. For example: --A method of detecting the presence of a ligand by detecting a change in the (optical) signal from a signaling aptamer comprising a reporter molecule (fluorescent dye) wherein the change in signal results from (or: is transduced by) a change in conformation of the signaling aptamer on binding the ligand...-- Cf. claims 4 and 5, 17 and 18.

(c) In the "contacting" step "wherein" is grammatically incorrect. It is suggested to replace it with --under conditions whereby--.

(d) In the "detecting" step "thereby transducing the conformational change" does not flow from "detecting". It is suggested to recite --thereby confirming transduction of the conformation change in the signaling aptamer to the differential signal of the reporter molecule--. Alternatively, recite --detecting the optical signal generated by the fluorescent dye transduced by the conformational change of the signaling aptamer upon binding the ligand--, deleting the "thereby" clause.

(e) In claims 4 and 5 the introduced "nucleic acid binding species (aptamer)" is confusing because it describes a ligand. It is suggested to change "ligand" to --ligand-binding-- or, preferably, --ligand-binding nucleic acid--. Furthermore, "species" is confusing in that the implied genus, nucleic acids or aptamers, is unclear.

(f) In claims 4 and 5 the introduced "nucleic acid binding species (aptamer)" is confusing because it lacks antecedent basis in claims 1 and 4, respectively, and appears to be an attempt to define "aptamer". If the latter, it should be recited in the first claim.

(g) In claim 10 "wherein the aptamer is not a...biopolymer" is confusing because aptamers are nucleic acids which are often referred to as "polymers". Furthermore, "biopolymer" in the context of the claimed invention is not defined in the claims or in the

specification such that one of skill in the art would have been apprised of the scope of the claimed invention.

(h) Claim 28 is confusing in being in improper dependent format because claim 15 is drawn to a method, not to a "ligand", a "signaling aptamer" or an "optical signal". It is suggested to either rewrite claim 28 as an independent claim or as --The method of claim 15 wherein the ligand is quantitated by the steps of: (etc.)--.

(I) Claim 28 lacks proper antecedent basis in claim 15 for "the increase in the optical signal" because claim 15 does not recite an "increase in optical signal" and on the contrary, claim 15 indicates that the optical signal is only produced ("generated") when the signaling aptamer changes conformation on binding the ligand. It is suggested to rectify the difference between the two claims.

Rejections under 102(b): Anticipation

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1-13, 15-17, 19, 23, 25 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by the patent to Pitner et al. (5,650,275). Regarding claim 1, Pitner et al. disclose the claimed invention method of detecting a differential signal of a signaling aptamer (detectably labeled nucleic acid ligand) upon binding a ligand (target compound), the differential signal generated by a reporter molecule (spectroscopically detectable label) comprising the steps of contacting (mixing) the signaling aptamer (spectroscopically detectably labeled nucleic acid ligand) with the ligand (target compound) wherein the former binds (complexes with) the latter and detecting the differential signal generated by the reporter molecule (spectroscopically detectable label measured before and after binding)) at columns 13-14, claim 1. The instant claim recitation "transducing the conformational change of a signaling aptamer upon binding a ligand to a differential signal" is inherent in the claim 1 method of Pitner et al. because it was known in the prior art as set forth in the "Description of the Related Art" section of the instant specification that aptamers (nucleic

acid ligands) "undergo an 'induced fit' conformational change in the presence of their cognate ligands, and thus an appended dye easily undergoes a ligand-dependent change in its local environment". *In re Spada*, 911F.2d 705, 15 USPQ2d 1650 (Fed. Cir. 1990). (Inherency of property or method steps in reference. MPEP 2112.01) Also see Pitner et al. at column 2, lines 55-59).

Regarding claims 2, 3, 7-9, Pitner et al. disclose the claimed method embodiment wherein the differential signal comprises an optical signal which is fluorescence, polarization or lifetime wherein the reporter molecule is a fluorescent dye and the latter is fluorescein (column 3, line 64-column 4, line 7; column 4, lines 56-59).

Regarding claims 4-6, Pitner et al. disclose the claimed method embodiment wherein the signaling aptamer comprises a reporter molecule appended to a nucleic acid binding species (nucleic acid ligand) at column 14, claims 3-4; and the reporter molecule is appended to the nucleic acid binding species (nucleic acid ligand) by covalent coupling (column 4, lines 21-27) during chemical synthesis (column 4, lines 28-43).

Regarding claims 10-13, Pitner et al. disclose the claimed method embodiment wherein the aptamer (nucleic acid ligand) is DNA which is not a protein (column 8, Example 2); the ligand (target compound) is not a nucleic acid (column 3, lines 23-48); the ligand (target compound) is in solution and the signaling aptamer (labeled nucleic acid ligand) is in solution (columns 9-10, Example 3).

Regarding claim 15, Pitner et al. disclose the claimed invention method of detecting an optical signal of a signaling aptamer (detectably labeled nucleic acid ligand) upon binding a ligand (target compound), the optical signal generated by a fluorescent dye comprising the steps of contacting (mixing) the signaling aptamer (fluorescently labeled nucleic acid ligand) with the ligand (target compound) wherein the former binds (complexes with) the latter and detecting the optical signal generated by the fluorescent dye (measured before and after binding)) at columns 13-14, claim 1 and column 3, line 64- column 4, line 7. The instant claim recitation "transducing the conformational change of a signaling aptamer upon binding a ligand to a differential signal" is inherent in the claim 1 method of Pitner et al. because it was known in the prior art as set forth in the "Description of the Related Art" section of the instant specification that aptamers (nucleic acid ligands) "undergo an 'induced fit'

conformational change in the presence of their cognate ligands, and thus an appended dye easily undergoes a ligand-dependent change in its local environment". *In re Spada*, 911F.2d 705, 15 USPQ2d 1650 (Fed. Cir. 1990). (Inherency of property or method steps in reference. MPEP 2112.01) Also see Pitner et al. at column 2, lines 55-59).

Regarding claims 16, 17 and 19 Pitner et al. disclose the claimed method embodiments wherein the optical signal is fluorescence, polarization or lifetime, the fluorescent dye is appended to a nucleic acid binding species (aptamer) (nucleic acid ligand) by covalent coupling (column 4, lines 21-27); and the fluorescent dye is fluorescein (column 3, line 64-column 4, line 1).

Regarding claim 23, Pitner et al. disclose the claimed method embodiment wherein the ligand (target compound) is a molecule bound by the signaling aptamer wherein the molecule is not a nucleic acid (column 3, lines 23-48)

Regarding claims 25 and 26, Pitner et al. disclose the claimed method embodiment wherein the ligand (target compound) is in solution and the signaling aptamer (labeled nucleic acid ligand) is in solution (columns 9-10, Example 3).

5. Claims 1-13, 15-17, 19, 23, 25, 26 and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by the patent to Royer (5,445,935). Regarding claim 1, Royer discloses the claimed invention method of detecting a differential signal of a signaling aptamer (fluorescent labeled polynucleotide) upon binding a ligand (macromolecule), the differential signal generated by a reporter molecule (fluorescent label) comprising the steps of contacting the signaling aptamer (fluorescent labeled polynucleotide) with the ligand (macromolecule) wherein the former binds (complexes with) the latter and detecting the differential signal generated by the reporter molecule (fluorescent label measured before and after binding)) at column 17, claim 1. The instant claim recitation "transducing the conformational change of a signaling aptamer upon binding a ligand to a differential signal" is inherent in the claim 1 method of Royer because it was known in the prior art as set forth in the "Description of the Related Art" section of the instant specification that aptamers (nucleic acid ligands) "undergo an 'induced fit' conformational change in the presence of their cognate ligands, and thus an appended dye easily undergoes a ligand-dependent change in its local environment". *In re Spada*, 911F.2d 705, 15 USPQ2d 1650 (Fed. Cir.

1990). (Inherency of property or method steps in reference. MPEP 2112.01) Also see Pitner et al. at column 2, lines 55-59).

Regarding claims 2, 3, 7-9, Royer discloses the claimed method embodiment wherein the differential signal comprises an optical signal which is fluorescence polarization wherein the reporter molecule is a fluorescent dye and the latter is fluorescein (column 17, claims 1 and 2).

Regarding claims 4-6, Royer discloses the claimed method embodiment wherein the signaling aptamer comprises a reporter molecule appended to a nucleic acid binding species (polynucleotide) and the reporter molecule is appended to the nucleic acid binding species by covalent coupling during chemical synthesis (column 6, lines 34-45).

Regarding claims 10-13, Royer. discloses the claimed method embodiment wherein the aptamer (polynucleotide) is DNA which is not a protein (column 1, line 68-column 2, line 4); the ligand (macromolecule) is not a nucleic acid (column 1, lines 63-65); the ligand is in solution and the signaling aptamer is in solution (column 2, lines 66-68).

Regarding claim 15, Royer discloses the claimed invention method of detecting an optical signal of a signaling aptamer (fluorescent labeled polynucleotide) upon binding a ligand (macromolecule), the optical signal generated by a fluorescent dye comprising the steps of contacting the signaling aptamer (fluorescent labeled polynucleotide) with the ligand (macromolecule) wherein the former binds (complexes with) the latter and detecting the optical signal generated by the fluorescent dye (measured before and after binding)) at column 17, claim 1. The instant claim recitation "transducing the conformational change of a signaling aptamer upon binding a ligand to a differential signal" is inherent in the claim 1 method of Pitner et al. because it was known in the prior art as set forth in the "Description of the Related Art" section of the instant specification that aptamers (nucleic acid ligands) "undergo an 'induced fit' conformational change in the presence of their cognate ligands, and thus an appended dye easily undergoes a ligand-dependent change in its local environment". *In re Spada*, 911F.2d 705, 15 USPQ2d 1650 (Fed. Cir. 1990). (Inherency of property or method steps in reference. MPEP 2112.01) Also see Pitner et al. at column 2, lines 55-59).

Regarding claims 16, 17 and 19 Royer discloses the claimed method embodiments wherein the optical signal is fluorescence polarization, the fluorescent dye is appended to a nucleic acid binding species (aptamer) (polynucleotide) by covalent coupling (column 6, lines 43-45); and the fluorescent dye is fluorescein (column 17, claim 2).

Regarding claim 23, Royer discloses the claimed method embodiment wherein the ligand (macromolecule) is a molecule bound by the signaling aptamer wherein the molecule is not a nucleic acid (column 1, lines 63-65).

Regarding claims 25 and 26, Royer discloses the claimed method embodiment wherein the ligand (macromolecule) is in solution and the signaling aptamer (fluorescent labeled polynucleotide) is in solution (column 2, lines 66-68).

Regarding claim 28, Royer discloses the claimed method embodiment for quantitating the ligand (macromolecule) of claim 15 wherein the signaling aptamer (fluorescent labeled polynucleotide) binds the ligand and the increase in the optical signal generated by the fluorescent dye resulting from the binding wherein the optical signal positively correlates with the quantity of ligand bound to the signaling aptamer at column 17, claim 1, column 19, lines 8-10, Abstract, lines 9-12.

Rejections under 102(e): Anticipation

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent

6. Claims 1-4, 7-17, 19, 23 and 25-27 are rejected under 35 U.S.C. 102(e) as being anticipated by the patent to Gold et al. (6,242,246). Regarding claims 1 and 15, Gold et al. disclose the claimed invention method of detecting a differential signal of a signaling aptamer (detectably labeled nucleic acid ligand) upon binding a ligand (target molecule), the differential signal generated by a reporter molecule (fluorescent label) comprising the steps of contacting the signaling aptamer (fluorescent labeled nucleic acid ligand) with the ligand (target molecule) wherein the former binds the latter and detecting the differential signal

generated by the reporter molecule (measured before and after binding)) in the Abstract, lines 2-14, column 15, lines 49-53 and column 16, lines 54-57. The instant claim recitation "transducing the conformational change of a signaling aptamer upon binding a ligand to a differential signal" is inherent in the claim 1 method of Gold et al. because it was known in the prior art as set forth in the "Description of the Related Art" section of the instant specification that aptamers (nucleic acid ligands) "undergo an 'induced fit' conformational change in the presence of their cognate ligands, and thus an appended dye easily undergoes a ligand-dependent change in its local environment". *In re Spada*, 911F.2d 705, 15 USPQ2d 1650 (Fed. Cir. 1990). (Inherency of property or method steps in reference. MPEP 2112.01) Also see Gold et al. at column 15, lines 49-52 and column 16, lines 54-56 and Pitner et al. at column 2, lines 55-59).

Regarding claims 2, 3, 7-9, 16, 17 and 19, Gold et al. disclose the claimed method embodiment wherein the differential signal comprises an optical signal which is fluorescence, polarization or lifetime wherein the reporter molecule is a fluorescent dye and the latter is fluorescein (column 15, lines 49-53).

Regarding claim 4, Gold et al. disclose the claimed method embodiment wherein the signaling aptamer comprises a reporter molecule appended to a nucleic acid binding species (nucleic acid ligand) (column 7, lines 39-41).

Regarding claims 10-13, 23, 25 and 26, Gold et al. disclose the claimed method embodiment wherein the aptamer (nucleic acid ligand) is RNA, DNA, modified RNA or modified DNA which is not a protein (column 5, paragraph at 4.); the ligand (target molecule) is not a nucleic acid (column 6, lines 2-4); the ligand (target molecule) is in solution and the signaling aptamer (labeled nucleic acid ligand) is in solution (column 9, lines 10-13).

Regarding claims 13, 14, 26 and 27, Gold et al. disclose the claimed method embodiment wherein the signaling aptamer (labeled nucleic acid ligand) is immobilized on a solid support in parallel wherein the immobilization forms signaling aptamer (labeled nucleic acid ligand) chips in the Abstract and at columns 9-10.

Rejections under 35 U.S.C. 103(a): Obviousness

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 14, 18, 20-22, 24 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pitner et al. (5,650,275) as applied to claims 1-13, 15-17, 19, 23, 25, 26 and 28 above (paragraph 4), and further in view of Gold et al. (6,242,246), Conrad (5,728,525) and Szostak et al. (5,631,146). Regarding claims 14 and 27, the claimed invention method of these claims differs from the method of Pitner et al. wherein the signaling aptamer (detectably labeled nucleic acid ligand) is immobilized on a solid support in parallel wherein the immobilization forms signaling aptamer chips. However, Gold et al. teach the method of instant claim 1 and of Pitner et al. claim 1 wherein the detectably labeled nucleic acid ligand (signaling aptamer) is immobilized on a solid support in parallel wherein the immobilization forms signaling aptamer (labeled nucleic acid ligand) chips (Abstract and columns 9-10). It would have been obvious and the skilled practitioner in the art would have been motivated at the time the claimed invention was made to immobilize the detectably labeled nucleic acid ligands (signaling aptamer) in view of the teaching of Pitner et al. that for detecting a target molecule spectroscopically detectably labeled nucleic acid ligands (signaling aptamers) may be used in solid or liquid form (column 5, lines 65-68) and the teaching of Gold et al. of the advantage of detectably labeled nucleic acid ligands (signaling aptamers) immobilized on chips for identifying simultaneously an "extremely large number of Nucleic acid ligands that recognize correspondingly large numbers of Targets in a biological sample" (column 8, lines 41-46).

Regarding claim 18, the claimed method embodiment differs from the method of Pitner et al. wherein the fluorescent dye replaces a nucleic acid residue in the aptamer or is inserted between two nucleic acid residues in the aptamer wherein the placement does not interfere with the ligand-binding site of the aptamer. However, it was known in the art as taught by Conrad to substitute a fluorescent dye for a nucleic acid residue in a

polynucleotide during chemical or enzymatic synthesis (column 12, lines 46-63). It would have been obvious and the skilled practitioner in the art would have been motivated at the time the claimed invention was made to label the nucleic acid ligand of Pitner et al. by replacing a nucleic acid residue with a fluorescent dye by the obvious benefit of ease and economy of labor in replacing the residue during chemical or enzymatic synthesis.

Regarding claims 20-22 and 24, the claimed method embodiment differs from the method of Pitner et al. wherein the aptamer (nucleic acid ligand) is an anti-adenosine RNA or DNA aptamer wherein the former is ATP-R-Ac13 and the latter is DFL7-8 and the ligand (target molecules) is adenosine. However, Pitner et al. note that numerous nucleic acid ligands that bind target molecules have been identified and cite a paper by Sassanfar and Szostak disclosing anti-adenosine triphosphate nucleic acid ligands (RNA aptamers) and the Szostak et al. patent teaches anti-adenosine triphosphate and anti-adenosine DNA aptamers prepared by the same process (column 4, line 56-column 5, line 9). It would have been obvious and the skilled practitioner in the art would have been motivated at the time the claimed invention was made to employ an anti-adenosine aptamer in the method of Pitner et al. in view of the Pitner et al. teaching such aptamers (nucleic acid ligands) were known in the art and in view of the known benefit of employing an aptamer that was known and proven in the art and readily obtainable by synthesis of the published nucleotide sequence. It would have been obvious further to synthesize aptamer analogues of the claims 21 and 22 aptamers in view of the teaching of Szostak et al. of a large number of anti-adenosine aptamers having the same conserved region as the aptamer of claim 22 (Figure 4A) and the methods for producing them wherein such aptamers would have been expected by one of ordinary skill in the art to function in the same manner as the aptamers of claims 21 and 22 in view of the reference teaching that the conserved regions are the critical adenosine binding regions (column 7, lines 29-35 and column 8, lines 47-52).

8. Claim 28 is rejected under 35 U.S.C. 103(a) as being unpatentable over Pitner et al. (5,650,275) as applied to claims 1-13, 15-17, 19, 23, 25, 26 and 28 above (paragraph 4), and further in view of Royer (5,445,935). The claimed method embodiment of claim 28 differs from the method of Pitner et al. wherein the ligand (target molecule) of claim 15 is quantitated by a method wherein the signaling aptamer (fluorescent labeled nucleic acid

ligand) binds the ligand and the increase in the optical signal generated by the fluorescent dye resulting from the binding positively correlates with the quantity of ligand bound to the signaling aptamer. However, Royer teaches a method for quantitating a ligand (macromolecule) wherein a fluorescent labeled polynucleotide (signaling aptamer) binds the macromolecule (ligand) and the increase in the optical signal generated by the fluorescent dye resulting from the binding wherein the optical signal positively correlates with the quantity of ligand bound to the signaling aptamer at column 17, claim 1, column 19, lines 8-10, Abstract, lines 9-12. It would have been obvious and the skilled practitioner in the art would have been motivated at the time the claimed invention was made to combine the quantitative method of Royer with the method of Pitner et al. in view of the teaching of Pitner et al. that their method can be used to quantitatively determine the presence of a target molecule (ligand) (column 3, lines 1-2 and column 4, lines 63-66) and further in view of the similarity of the Royer and Pitner et al. methods with regard to the binding (complexing) of a macromolecule (target molecule) with a fluorescently labeled polynucleotide (nucleic acid ligand) and the measuring of fluorescence polarization.

Conclusion

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephanie Zitomer whose telephone number is (703) 308-3985. The examiner can normally be reached on Monday through Friday from 9:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152. The official fax phone number for this Group is (703) 308-4242. The unofficial fax number is (703) 308-8724. The examiner's Rightfax number is 703-746-3148.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196. For questions and requests relating to formal matters contact Patent Analyst Tiffany Tabb at 703-605-1238.

Stephanie Zitomer, Ph.D.
March 25, 2002

PRIMARY EXAMINER